

(19)



(11)

EP 1 717 235 A3

(12)

EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
28.02.2007 Bulletin 2007/09

(43) Date of publication A2:
02.11.2006 Bulletin 2006/44

(21) Application number: **05291793.7**

(22) Date of filing: **26.08.2005**

(51) Int Cl.:
C07D 295/088 ^(2006.01) *C07D 213/30* ^(2006.01)
C07D 211/68 ^(2006.01) *C07D 333/16* ^(2006.01)
C07D 211/14 ^(2006.01) *C07D 401/10* ^(2006.01)
A61K 31/40 ^(2006.01) *A61K 31/44* ^(2006.01)
A61K 31/381 ^(2006.01) *A61K 31/5377* ^(2006.01)
A61P 25/00 ^(2006.01)

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI
SK TR**
Designated Extension States:
AL BA HR MK YU

(30) Priority: **29.04.2005 EP 05290950**

(71) Applicant: **BIOPROJET**
75003 Paris (FR)

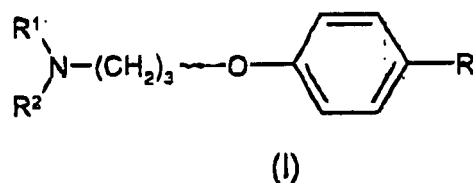
(72) Inventors:
 • **Bertrand, Isabelle**
35740 Pace (FR)
 • **Capet, Marc**
35520 Melesse (FR)

- **Lecomte, Jeanne-Marie**
75003 Paris (FR)
- **Levain, Nicolas**
35310 Mordelle (FR)
- **Ligneaux, Xavier**
35760 Saint Gregoire (FR)
- **Poupardin-Olivier, Olivia**
35830 Betton (FR)
- **Robert, Philippe**
35740 Pace (FR)
- **Schwartz, Jean-Charles**
75014 Paris (FR)

(74) Representative: **Colombet, Alain André et al**
Cabinet Lavoix,
2, Place d'Estienne d'Orves
75441 Paris Cedex 09 (FR)

(54) **Phenoxypropylpiperidines and -pyrrolidines and their use as histamine H3-receptor ligands**

(57) The present patent application concerns compounds of formula (I),



with R¹ and R² taken together with the nitrogen atom to which they are attached, form a mono or bicyclic saturated nitrogen-containing ring;
 their preparation and their use as a H3 receptor ligand for treating e.g. CNS disorders like Alzheimer's disease.

EP 1 717 235 A3



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 05 29 1793

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
D,X	WO 00/06254 A (SOCIETE CIVILE BIOPROJET; SCHWARTZ, JEAN-CHARLES; ARRANG, JEAN-MICHEL;) 10 February 2000 (2000-02-10) * claims 1,4-7,16,18,23,24,26,79-87; examples 44,48,59,65,74,90,93,96,104,111 * * page 55, line 15 - page 56, line 25 *	1-3,5, 11, 14-20, 23,25	INV. C07D295/088 C07D213/30 C07D211/68 C07D333/16 C07D211/14 C07D401/10 A61K31/40
X	WO 2004/037788 A (GLAXO GROUP LIMITED; BEST, DESMOND, JOHN; ORLEK, BARRY, SIDNEY) 6 May 2004 (2004-05-06) * claims 1,4,6,8,11,12,23; examples 1-4,8-65 * * page 9, line 11 - line 25 *	1,2,11, 14-23,25	A61K31/44 A61K31/381 A61K31/5377 A61P25/00
X	WO 02/076925 A (ELI LILLY AND COMPANY; BEAVERS, LISA, SELSAM; GADSKI, ROBERT, ALAN; HI) 3 October 2002 (2002-10-03) * claims 1,7,14,21,22; examples 216,227,236,269,270,297-301 * * page 1, line 6 - line 22 *	1-3,5, 13, 15-23,25	
X	US 4 950 674 A (YANNI ET AL) 21 August 1990 (1990-08-21) * abstract; examples 53,90,182; table 1 *	1,3,5, 14,15,25	TECHNICAL FIELDS SEARCHED (IPC) C07D A61K
X	KUBOTA, HIDEKI ET AL.: J. MED. CHEM., vol. 46, 2003, pages 4728-4740, XP002355168 * page 4729; table 2; compound 10S *	1,3,14, 15	
----- -/--			
6 The present search report has been drawn up for all claims			
Place of search Berlin		Date of completion of the search 15 August 2006	Examiner Krische, Detlef
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

EPO FORM 1503 03.82 (P04C01)



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 05 29 1793

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 99/59959 A (ZENECA LIMITED; BROWN, DEARG, SUTHERLAND; BROWN, GEORGE, ROBERT) 25 November 1999 (1999-11-25) * example 5; table I; compound 3 * * example 6 * * example 7; table II; compounds 38,41,42 * * page 54, line 16 - line 20 * -----	1,2,13, 15,25	TECHNICAL FIELDS SEARCHED (IPC)
X	EP 0 382 185 A (OTSUKA PHARMACEUTICAL CO., LTD) 16 August 1990 (1990-08-16) * abstract * * examples 111,115,332; table 1 * * examples 450-456; table 3 * -----	1,3,15	
X	YOSHIDA K ET AL: "Synthesis of Benzanilide Derivatives as Dual Acting Agents with alpha1-Adrenoceptor Antagonistic Action and Steroid 5-alpha Reductase Inhibitory Activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 21, 3 November 1998 (1998-11-03), pages 2967-2972, XP004141855 ISSN: 0960-894X * abstract; figure 1; compound 1 * * table 1; compound 5C * * scheme 1 * -----	1,14,15	
X	WO 2004/037800 A (GLAXO GROUP LIMITED; BEST, DESMOND, JOHN; BRUTON, GORDON; HEIGHTMAN, T) 6 May 2004 (2004-05-06)	1-3,11, 14-23,25	
Y	* claim 1; examples 1-51,57-114,123,124,147-152,156-162,172 * * page 17, line 30 - page 18, line 13 * * page 8, line 30 - page 10, line 25 * ----- -/-	24,26	
<div style="border: 1px solid black; padding: 5px;"> <p>The present search report has been drawn up for all claims</p> </div>			
Place of search Berlin		Date of completion of the search 15 August 2006	Examiner Krische, Detlef
<div style="display: flex; justify-content: space-between;"> <div> <p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>O : non-written disclosure</p> <p>P : intermediate document</p> </div> <div> <p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p> </div> </div>			

6

EPO FORM 1503 03-82 (P04C01)



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 05 29 1793

DOCUMENTS CONSIDERED TO BE RELEVANT				
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)	
Y	WO 03/059342 A (ABBOTT LABORATORIES) 24 July 2003 (2003-07-24) * page 1, line 3 - line 5; claim 1 *	24		
Y	WO 01/74815 A (ORTHO MCNEIL PHARMACEUTICAL, INC) 11 October 2001 (2001-10-11) * page 1, line 21 - page 2, line 6 *	26		
E	WO 2005/089747 A (SERVIER LAB [FR]; CASARA PATRICK [FR]; CHOLLET ANNE-MARIE [FR]; DHAINA) 29 September 2005 (2005-09-29) * abstract; claims 1,8,12,13,23,24,31-36; examples 6,9,11-15,17,22,51,52,57-61,84-93,104-106 * * page 48, line 4 - line 10 *	1,3,5, 11, 14-21, 23,25		
E	WO 2005/100321 A (MILLENNIUM PHARMACEUTICALS, INC; GHOSH, SHOMIR; ELDER, AMY, M; CARSON,) 27 October 2005 (2005-10-27) * table 3; compounds C103, C104 * * table 9; compounds H28,H76,H118,H129,H132,H149 * * page 44, paragraph 147 *	1,11,13, 15,25		TECHNICAL FIELDS SEARCHED (IPC)
A	PESCHKE, BERND ET AL.: BIOORGANIC & MEDICINAL CHEMISTRY, vol. 12, 2004, pages 2603-2616, XP002355169 * abstract * * page 2609 - page 2610 *	16		
A	HILTMANN, R. ET AL.: SYNTHESIS, 1971, pages 213-214, XP002355170 * the whole document *	1		
<p>The present search report has been drawn up for all claims</p>				
Place of search Berlin		Date of completion of the search 15 August 2006	Examiner Krische, Detlef	
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>				

6
EPO FORM 1503 03.82 (P04C01)

**CLAIMS INCURRING FEES**

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1-3, 5, 7, 9, 11-26 in part



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-3,5,7,9,11-26 in part

Compounds of formula (I) having a -CONR³R⁴ group as substituent R for use as H₃-receptor ligands; their preparation and use.

2. claims: 1-3,7,11-26 in part

Compounds of formula (I) having a benzoyl group as substituent R for use as H₃-receptor ligands; their preparation and use.

3. claims: 1-3,5-7,9-26 in part

Compounds of formula (I) having a -C(OH)R⁵R⁶ group as substituent R for use as H₃-receptor ligands; their preparation and use.

4. claims: 1-3,7,11-26 in part

Compounds of formula (I) having a -CH₂CN group as substituent R for use as H₃-receptor ligands; their preparation and use.

5. claims: 1-3,7,11-26 in part

Compounds of formula (I) having an isoprenyl group as substituent R for use as H₃-receptor ligands; their preparation and use.

6. claims: 1-3,7,11-26 in part

Compounds of formula (I) having a styryl group as substituent R for use as H₃-receptor ligands; their preparation and use.

7. claims: 1-3,7,11-26 in part

Compounds of formula (I) having a phenoxy or benzyloxy group as substituent R for use as H₃-receptor ligands; their preparation and use.

8. claims: 1-26 in part



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Compounds of formula (I) having a partially saturated nitrogen containing heterocycle or a nitrogen containing heteroaryl as substituent R for use as H3-receptor ligands; their preparation and use.

9. claims: 1-3,7,11-26 in part

Compounds of formula (I) having a thienyl group as substituent R for use as H3-receptor ligands; their preparation and use.

10. claims: 1-26 in part

Compounds of formula (I) having a phenyl group as substituent R for use as H3-receptor ligands; their preparation and use.

11. claims: 1-26 in part

Compounds of formula (I) having a saturated cycloalkyl group as substituent R for use as H3-receptor ligands; their preparation and use.

12. claims: 1,2,7,11-26 in part

Compounds of formula (I) having an alkyl group substituted by a cycloalkyl group as substituent R for use as H3-receptor ligands; their preparation and use.

13. claims: 1-3,5,7,9,11-26 in part

Compounds of formula (I) having an -alkyl-phenyl-(O)_n-X-NR₃R₄ group as substituent R for use as H3-receptor ligands; their preparation and use.

14. claims: 1,2,7,11-26 in part

Compounds of formula (I) having an alkenyl or alkynyl group substituted by -(CO)-NR₃R₄ as substituent R for use as H3-receptor ligands; their preparation and use.

15. claims: 1,2,7,11-26 in part



European Patent
Office

**LACK OF UNITY OF INVENTION
SHEET B**

Application Number

EP 05 29 1793

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Compounds of formula (I) having a phenylalkyl, phenylalkenyl or phenylalkynyl group substituted by $-(CO)_n-NR_3R_4$ as substituent R for use as H₃-receptor ligands; their preparation and use.

16. claims: 27,28

Process for preparing intermediate compound of formula (X)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 05 29 1793

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-08-2006

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0006254	A	10-02-2000	AT 326446 T	15-06-2006
			AT 276751 T	15-10-2004
			AU 5511999 A	21-02-2000
			CA 2321881 A1	10-02-2000
			DE 69920472 D1	28-10-2004
			DE 69920472 T2	06-10-2005
			DE 69931409 T2	02-11-2006
			EP 0982300 A2	01-03-2000
			ES 2260703 T3	01-11-2006
			ES 2226423 T3	16-03-2005
			JP 2002521463 T	16-07-2002
			PT 1428820 T	29-09-2006
			PT 1100503 T	31-01-2005
			US 7138413 B1	21-11-2006
WO 2004037788	A	06-05-2004	AT 346044 T	15-12-2006
			AU 2003278119 A1	13-05-2004
			EP 1554243 A1	20-07-2005
			JP 2006505623 T	16-02-2006
WO 02076925	A	03-10-2002	AU 2002254114 A1	08-10-2002
			CA 2441080 A1	03-10-2002
			EP 1379493 A2	14-01-2004
			JP 2004532834 T	28-10-2004
US 4950674	A	21-08-1990	NONE	
WO 9959959	A	25-11-1999	AT 282590 T	15-12-2004
			AU 749293 B2	20-06-2002
			AU 3939999 A	06-12-1999
			BR 9910474 A	02-01-2001
			CA 2328927 A1	25-11-1999
			CN 1300278 A	20-06-2001
			DE 69921986 D1	23-12-2004
			DE 69921986 T2	22-12-2005
			EP 1077931 A1	28-02-2001
			ES 2232137 T3	16-05-2005
			HK 1033754 A1	06-05-2005
			HU 0102295 A2	28-11-2001
			ID 26236 A	07-12-2000
			JP 2002515476 T	28-05-2002
			NO 20005767 A	14-11-2000
			NZ 507144 A	25-10-2002
			PL 344164 A1	08-10-2001
			PT 1077931 T	31-03-2005
			RU 2215736 C2	10-11-2003

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 05 29 1793

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-08-2006

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9959959	A		SK 17182000 A3	10-05-2001
			TR 200003353 T2	20-04-2001
			US 6579872 B1	17-06-2003

EP 0382185	A	16-08-1990	CN 1046529 A	31-10-1990
			DE 69009785 D1	21-07-1994
			DE 69009785 T2	03-11-1994
			DK 382185 T3	04-07-1994
			ES 2056259 T3	01-10-1994
			HK 1003113 A1	09-10-1998

WO 2004037800	A	06-05-2004	AU 2003274053 A1	13-05-2004
			EP 1554260 A1	20-07-2005
			JP 2006512404 T	13-04-2006
			US 2006052597 A1	09-03-2006

WO 03059342	A	24-07-2003	AU 2003235687 A1	30-07-2003
			CA 2473232 A1	24-07-2003
			EP 1474132 A1	10-11-2004
			JP 2006500315 T	05-01-2006
			MX PA04006777 A	10-11-2004
			US 2005113435 A1	26-05-2005

WO 0174815	A	11-10-2001	AU 4967901 A	15-10-2001
			EP 1268478 A2	02-01-2003

WO 2005089747	A	29-09-2005	AR 047685 A1	01-02-2006
			AU 2005224129 A1	29-09-2005
			CA 2555216 A1	29-09-2005
			EP 1720544 A1	15-11-2006
			FR 2866647 A1	26-08-2005

WO 2005100321	A	27-10-2005	AR 048528 A1	03-05-2006
			AU 2005233125 A1	27-10-2005
			CA 2561564 A1	27-10-2005
